

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Mauriac et al. Confirmation No.: 8762
Serial No.: 10/562,763 Art Unit: 1615
Filed: December 27, 2005 Examiner: Helm Caralynne E.
Attorney Docket No.: 207,388
Title: "Subcutaneous implants having limited initial release of the active principle and subsequent linearly varying extended release thereof"

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Applicants request review of the final rejection in the above identified application. No amendments are being filed with this request. This request is being filed with a Notice of Appeal. The review is requested for the reasons stated below. Claims 22-26, 28-29 and 31-34 are pending and stand rejected.

1. Rejection under 35 U.S.C. §103(a) as being obvious over Chou et al. (US 2004/0009222) in view of Wang et al. (Pharm. Res. 1996, 13(7):1059-1064)

1.1. Wang et al. teach away from the claimed invention

According to the Examiner (p. 14, Office Action, December 20, 2010, "OA4"), "Chou et al. envision embodiments where the skin partially covers its core, thereby leaving an opening like that taught in Wang et al.. Moreover, the instant claims do not exclude the presence of a hole or opening in the PLGA skin."

Wang et al. was first discussed by the Examiner in the Office Action dated September 29, 2008 (pp. 5-6, "OA1"), wherein claim 22 was rejected as being anticipated by Wang et al.. The Applicants overcame the rejection demonstrating (pp. 7-10, Reply, March 27, 2009) that Wang et al. indeed *teach away* from the current invention *in view of the opening drilled through the coating*. This line of argument was found persuasive by the Examiner who withdrew the rejection in the subsequent Office Action (June 16, 2009, "OA2"). Notably, the second OA was completely silent about Wang et al.. This is seen as an implicit admission that the Examiner considered the subcutaneous implants of claim 22 both new (since it has no hole in the coating), and non-obvious (teaching away) over Wang et al., in view of the arguments submitted by the Applicant in response to the first Office Action.

The Applicant submitted an amended version of claim 22 along with a reply to the first Office Action (OA1). Applicant's remarks, based on the "teaching away" argumentations, which applied to former claim 22, certainly remain valid and apply to the amended version of claim 22 as well, since it includes further limitations and has a scope of protection narrower than the former claim 22 (not amended).

Furthermore, assuming the implants disclosed by Wang et al. are modified to obtain a uniform coating showing no openings, this modification would render said implants unsatisfactory for the intended purpose of controlling the 5-fluorouracil (5-FU) release in the subconjunctival tissues, while minimizing the level of the same in other non-target ocular tissues. Wang et al. actually proved that said release is dependent on a number of aspects, i.e. the lactide/glycolide ratio in the PLGA, the drug loading, the coating, the hole anatomy and the hole dimensions (see e.g. abstract, Fig. 2 and Fig. 3). Considering that the Wang et al. coating has been found to be intact at the end of the release study (see p. 1061, par. "In vitro release"), it can be immediately understood that the absence of the hole in the coating would render the Wang et al. implants inoperable for their intended purposes (MPEP §2145), as well as it would change the principle of operation; this also counsels against a finding of obviousness. (MPEP §2143.01)

1.2. Claims 22, 25 and 31-32 are not obvious over Chou et al. in view of Wang et al.

Claims 22, 25 and 31-32 stand rejected over Chou et al. in view of Wang et al. (pp. 5-6, 13-15, OA4). An obviousness rejection requires that the Examiner establishes a *prima facie* case (MPEP §2142).

First, the ground of rejection is based on the Examiner's position that "Chou et al. envision embodiments where the skin partially covers its core, thereby leaving an opening like that taught in Wang et al. Moreover, the instant claims do not exclude the presence of a hole or opening in the PLGA skin. Thus the teachings of Chou et al. and Wang et al. are not inconsistent" (p. 14, OA4). As discussed above, Wang et al. not only fail to teach the limitations of claim 22, but also teach away from the current invention. The fact that a reference teaches away from the claimed invention is sufficient on its own to defeat a *prima facie* case of obviousness. See *Winner Int'l Royalty Corp. vs. Wang*, 202 F.3d 1340, 1349-50 (Fed Cir. 2000). Additionally, Chou et al. as well, fail to teach all the claimed limitations of claim 22, as acknowledged by the Examiner (p. 5, OA4). However, failing to consider references as a whole in making an obviousness rejection is an error on the part of the Examiner (MPEP §2141.02).

The Examiner has also provided no basis to support the allegation that "the instant claims do not exclude the presence of a hole or opening in the PLGA skin". In contrast, the Applicants already explained (p. 10, Reply, March 27, 2009) that the

term “coating” in claim 22 leaves no room for the possibility of a hole. This is also fully consistent with the description given in the specification for the elected invention.

Furthermore, it has already been demonstrated that the document of Chou et al. as a whole discourages one of skill in the art from considering desirable the combination of features claimed in claim 22. This represents an additional element which also discourages the making of a combination with Wang et al.. Specifically, the Applicants affirmed (pp. 12-13, Reply, March 27, 2009) that uncoated matrixes of PCL provide for a far better release profile with respect to uncoated matrixes of PLGA. For this reason, Chou et al. chose matrixes of PCL and teaches coating the same with PLGA skin. However, it is important to note that Chou et al. teach that only 15% of the drug is released after 2 months, while it is totally silent on the release of the remaining amount (85%) of the dose. Therefore, the following (delayed) phases of the release are definitely left unknown and completely unpredictable. The unpredictability is necessarily greatly increased for undisclosed combinations of polymers.

The Examiner also failed to provide any evidence or scientific reasoning underlying the allegation that Chou et al. gives a linear release profile over several months (p. 5, OA4) and Applicants have been unable to identify any teachings in Chou et al. supporting said assertion. Instead, it appears that the rejections of the Examiner were based merely on the content of the instant specification (e.g. Fig. 4B and Fig. 5B, Ex. 4 and Ex. 5) and on the evidence provided by Applicant with a Declaration submitted on March 27, 2009 and discussed at pages 13-15 of the accompanying Reply. It is an error for the Examiner to base any part of an obviousness rejection on **information only found in the Applicant’s specification or experimental evidence** provided by Applicants. (MPEP §2145)

For at least the reasons given above the rejection of Claims 22, 25 and 31-32 over Chou et al. in view of Wang et al. is improper and should be set aside.

2. Rejection under 35 U.S.C. §103(a) as being obvious over Maquin et al. in view of Chou et al. and Jain et al.

2.1. Maquin et al. fail to teach or suggest every limitation of the claimed invention

The Examiner improperly supports the obviousness rejection over Maquin et al. and fails to show that the claimed invention is taught or suggested by the art.

Maquin et al. discloses matrixes having a tri-phase release pattern i.e. showing not only a first burst but also an earlier and greater second burst, especially when the drug loading is reduced. These properties, which are well evident also from Figures 3 and 4 of the Maquin et al. reference, were already evidenced by the Applicants (p. 18, Reply, March 27, 2009). In contrast, the implants of claim 22 have “a limited initial release of the active principle and a subsequent linearly varying extended release”. These beneficial properties associated with the claimed coating demonstrate why this reference fails to teach or suggest the presently claimed invention. For at least this reason the obviousness rejection is improper and should be reversed.

2.2. Claims 22-25 are not obvious over Maquin et al. in view of Chou et al. and Jain et al.

The Examiner reiterated the opinion (pp. 9-10, OA4) that, in light of Jain et al., “it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the PLGA used in the drug core of the device taught by Maquin et al. in an outer skin as taught by Chou et al. to give additional control of the device release kinetics and reduce any burst that occurs.” However, the Examiner provided no evidence or scientific reasoning underlying this allegation and there are no teachings in the cited references supporting said assertion. Indeed, this rejection only includes conclusory statements and does not provide an articulated reasoning with some rational underpinning as to why the claimed invention would have been obvious. It should also be noted that, if Maquin et al. matrixes were **modified to be uniformly coated**, this modification would **render the matrixes unsatisfactory for their intended purpose** of increasing the total release time of peptides through a tri-phase release pattern (p. 4, lines 5-8, Maquin et al.). Considering that this pattern occurs because the Maquin et al. matrix directly contacts the aqueous environment (p. 4, lines 9-24, Maquin et al.), it can be immediately understood that the provision of a coating layer would render the Maquin et al. implants inoperable for their intended purposes (MPEP §2145), as well as would change the principle of operation: this also counsels against a finding of obviousness. (MPEP §2143.01)

Additionally, since it has already been demonstrated, and previously noted (§1.2.), that Chou et al. as a whole discourage the skilled artisan from considering the claimed combination of features desirable (pp. 12-13, Reply, March 27, 2009), and since Jain et al. only refer to uncoated matrixes comprising PLGA and proteins, the obviousness rejection is erroneous because there is no motivation to select and modify

the cited uncoated matrixes to achieve the claimed implants, much less with any reasonable expectation of success.

Actually, the Examiner has provided no reasoning or evidence to explain how one skilled in the art would have been expected to succeed in achieving an implant having “a limited initial release of the active principle and a subsequent linearly varying extended release” from an uncoated matrix having a tri-phase release pattern and even less how it is possible to combine said uncoated matrix having a tri-phase release pattern with Chou et al. whose teaching leaves the release of 85% of the dose absolutely undetermined. Because the Examiner has failed to factually support a *prima facie* case of obviousness, “an applicant is under no obligation to submit evidence of nonobviousness” MPEP §2142.

Instead, it appears that the Examiner has based her conclusion on the current specification (e.g. Fig. 4B and Fig. 5B, Ex. 4 and Ex. 5). It is an error for the Examiner to base any part of an obviousness rejection on information only found in the Applicant’s specification or on experimental evidence provided by the Applicant. (MPEP §2145)

In view of the above, and as supplemented by Applicants’ responses of record, the pending Claims are not obvious under any of the obviousness rejections posited. Withdrawal of all rejections is, therefore, respectfully requested and the issuance of a Notice of Allowance is respectfully solicited.

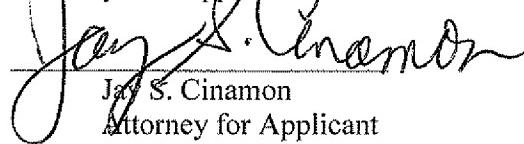
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Respectfully submitted,

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